

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. § 371		Attorney's Docket Number 054160-5060
International Application. No.	International Filing Date	U.S. Application No. <b>10/049666</b> Unassigned
PCT/EP00/08011	August 16, 2000	Priority Date Claimed August 16, 1999

Title of Invention: PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE DERIVATIVE AS  
ACTIVE INGREDIENT

Applicants For EO/EO/US: Tsuneji SUZUKI, Tomoyuki ANDO, Masahiko ISHIBASHI, Masahiro SAKABE  
and Ikuo SAKAI

Applicants herewith submit to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. § 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. § 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. § 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. § 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3)).
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)).
9. ☒ An oath or declaration of the inventors (35 U.S.C. § 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)).

Items 11. to 14. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 C.F.R. § 1.97 and § 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. § 3.28 and § 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☒ Other items or information:
  - a. PCT/IB/308
  - b. PCT/IPEA/409
  - c. PCT/ISA/210

U.S. APPLICATION NO. | INTERNATIONAL APPLICATION NO. | ATTORNEY DOCKET NUMBER

10/049666

Unassigned

PCT/EP00/08011

054160-5060

15.



The following fees are submitted:

**Basic National Fee (37 C.F.R. § 1.492(a)(1)-(5)):**

Search Report has been prepared by the EPO or JPO.....\$890.00

International preliminary examination fee paid to

USPTO (37 C.F.R. § 1.482).....\$710.00

No international preliminary examination fee paid to

USPTO (37 C.F.R. § 1.482) but international search fee

paid to USPTO (37 C.F.R. § 1.445(a)(2)).....\$740.00

Neither international preliminary examination fee

(37 C.F.R. § 1.482) nor international search fee

(37 C.F.R. § 1.445(a)(2)) paid to USPTO.....\$1,040.00

International preliminary examination fee paid to USPTO

(37 C.F.R. § 1.482) and all claims satisfied provisions

of PCT Article 33(2)-(4).....\$100.00

**ENTER APPROPRIATE BASIC FEE AMOUNT =**

\$890.00

Surcharge of \$130.00 for furnishing the oath or declaration later than

☐ 20 ☒ 30 months from the earliest claimed priority date

(37 C.F.R. § 1.492(e)).

\$

Claims	Number Filed	Number Extra	Rate	
Total Claims	36 - 20 =	16	X \$18.00	\$ 288.00
Independent Claims	1 - 3 =	0	X \$84.00	\$
Multiple dependent claim(s) (if applicable)			+ \$280.00	\$ 280.00
<b>TOTAL OF ABOVE CALCULATIONS</b>				\$ 1458.00
Reduction by ½ for filing by small entity, if applicable.				
Verified Small Entity statement must also be filed. (Note 37 C.F.R. §§ 1.9, 1.27, 1.28)				-\$
<b>SUBTOTAL =</b>				\$ 1458.00
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(f)).				+\$
<b>TOTAL NATIONAL FEE =</b>				\$ 1458.00
Fee for recording the enclosed assignment (37 C.F.R. § 1.21(h)).				
The Assignment must be accompanied by an appropriate cover sheet				
(37 C.F.R. §§ 3.28, 3.31). \$40.00 per property				\$ 40.00
<b>TOTAL FEES ENCLOSED =</b>				\$ 1498.00
Amount to be refunded				\$
Amount to be charged				\$ 1498.00

a.



Please charge Deposit Account No. 50-0310 in the amount of \$1498.00

to cover the above fees. A duplicate copy of this sheet is enclosed.

b.



**Except** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. § 1.16 and § 1.17 which may be required, or credit any overpayment to Deposit Account No. 50-0310.

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SEND ALL CORRESPONDENCE TO:

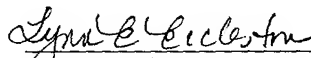
Morgan, Lewis &amp; Bockius LLP

1111 Pennsylvania Avenue, N.W.

Washington, D.C. 20004

Telephone: (202) 739-3000

Facsimile: (202) 739-3001



Lynn E. Eccleston

Reg. No. 35,861

Submitted: February 15, 2002

PATENT  
ATTORNEY DOCKET NO. 054160-5060

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of : Tsuneji SUZUKI et al. )  
)  
U.S. Application No.: To Be Assigned ) Group Art Unit: To Be Assigned  
)  
Date of National ) Examiner: To Be Assigned  
Stage Entry : February 15, 2002 )  
)  
Based on PCT/EP00/08011 )  
Filed : August 16, 2000 )  
)  
For: PHARMACEUTICAL AGENT )  
COMPRISING A BENZAMIDE )  
DERIVATIVE AS ACTIVE )  
INGREDIENT )

Commissioner for Patents  
Washington, D.C. 20231

Sir:

**PRELIMINARY AMENDMENT**

Prior to the examination of the above-identified application on the merits, please amend the application as follows:

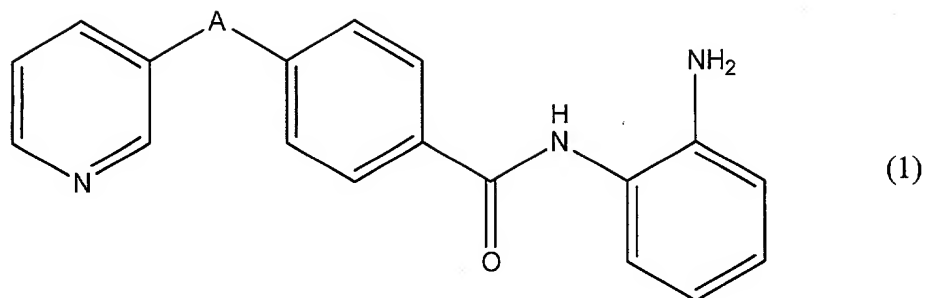
**In the claims:**

Please cancel claims 1-17.

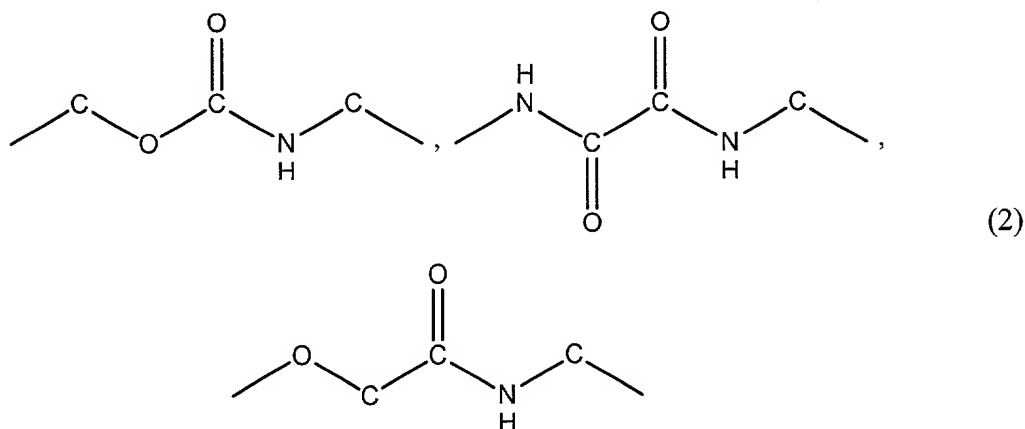
Please add the following claims 18-31:

18. A pharmaceutical composition, comprising: (a) a benzamide derivative represented by formula (1):

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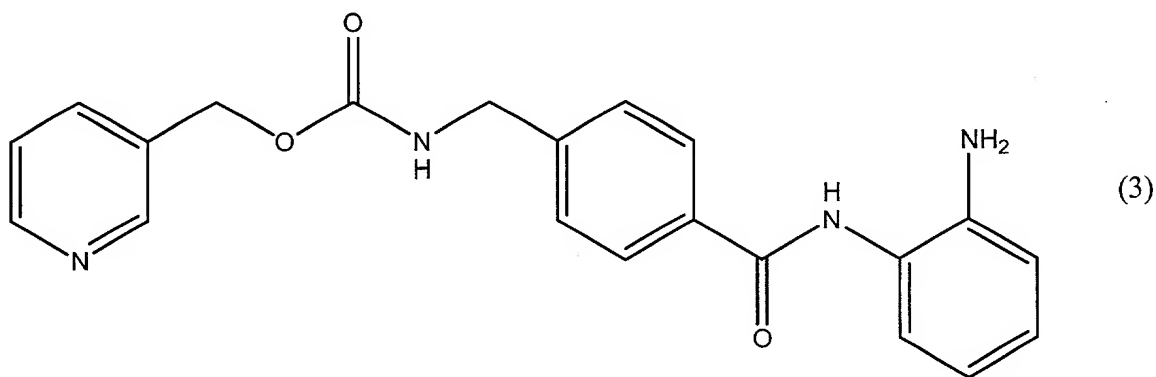


wherein A represents any one of the structures of formula (2):



or a pharmaceutically acceptable salt thereof, and (b) at least one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

19. The pharmaceutical composition according to claim 18, wherein said benzamide derivative is represented by formula (3):



20. The pharmaceutical composition according to claim 18, wherein said excipient is D-mannitol.

21. The pharmaceutical composition according to claim 18, wherein said disintegrant is at

least one disintegrant selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

22. The pharmaceutical composition according to claim 18, wherein said binder is hydroxypropyl cellulose.

23. The pharmaceutical composition according to claim 18, wherein said lubricant is at least one lubricant selected from the group consisting of magnesium stearate and talc.

24. The pharmaceutical composition according to claim 18, wherein said coating agent is hydroxypropyl methylcellulose.

25. The pharmaceutical composition according to claim 18, wherein said solvent is at least one solvent selected from the group consisting of a propylene glycol, dimethylacetamide, and polyethylene glycol.

26. The pharmaceutical composition according to claim 18, further comprising at least one compound selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance.

27. The pharmaceutical composition according to claim 26, wherein said organic acid salt is at least one organic acid salt selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

28. The pharmaceutical composition according to claim 26, wherein said amino compound is at least one amino compound selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine, L-glutamate, and carbachol.

29. The pharmaceutical composition according to claim 26, wherein said inorganic basic substance is at least one inorganic basic substance selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

30. The pharmaceutical composition according to any one of claims 18-29, wherein the pharmaceutical composition is a solid composition which comprises granules prepared by a dry granulation method.

31. The pharmaceutical composition according to any one of claims 18-29, wherein the pharmaceutical composition is a liquid composition with an adjusted pH ranging from about 4 to about 12.

**REMARKS**

Claims 1-17 in the application have been cancelled without waiver, disclaimer or prejudice. New claims 18-31 have been added by this Preliminary Amendment.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTION PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

**MORGAN, LEWIS & BOCKIUS LLP**



Lynn E. Eccleston

Reg. No. 35,861

Dated: February 15, 2002  
MORGAN, LEWIS & BOCKIUS LLP  
1111 Pennsylvania Avenue, N.W.  
Washington, D.C. 20004  
(202) 739-3000

## DESCRIPTION

PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE  
DERIVATIVE AS ACTIVE INGREDIENT

## 5 Field of Invention

The present invention relates to a pharmaceutical composition and in particular to a pharmaceutical formulations comprising as an active ingredient a benzamide derivative or a pharmaceutically acceptable salt thereof, that is useful as a pharmaceutical agent, in particular an anticancer agent.

## Background Art

Benzamide derivatives or pharmaceutically acceptable salts thereof according to the present invention have an ability of inhibiting histone deacetylating enzymes and of inducing differentiation, and are useful as therapeutic or ameliorating agents for diseases that are involved in cellular growth such as malignant tumors, autoimmune diseases, skin diseases, infections, blood vessel diseases, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants. In particular, they are effective as anti-tumor agents and are effective against hematopoietic organ tumors and solid tumors (Japanese Unexamined Patent Publication (Kokai) No. 10-152462).

However, though the benzamide derivatives and pharmaceutically acceptable salts thereof of the present invention are stable per se, they become unstable and decompose markedly over time when combined with additives such as light silicic acid anhydride, lactose, corn starch, carboxymethyl cellulose, magnesium alminate metasilicate, titanium oxide, polyethylene glycols and polysorbates that are commonly used in order to produce dosage forms suitable for oral, percutaneous, or tissue administration.

Furthermore, when they are formulated into tablets

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by the wet granulation, the most common granulation method of preparing solid formulations, they become further unstable and yield, in large quantities, decomposed products different from simple hydrolyzates, resulting in pharmaceutical formulations in which the ratio of an active ingredient is as low as about 0.001 to 25%, which noticeably decompose, and therefore which are unsuitable as pharmaceutical solid formulations to be provided as medical drugs. Also, pharmaceutical formulations that employ ingredients commonly used for liquids such as polysorbates, polyethylene glycols, and glycerin were unstable. Thus it was difficult to use, as medical drugs, pharmaceutical formulations that contain a benzamide derivative or a pharmaceutically acceptable salt thereof at about 0.001 to 25% as an active ingredient.

#### Disclosure of Invention

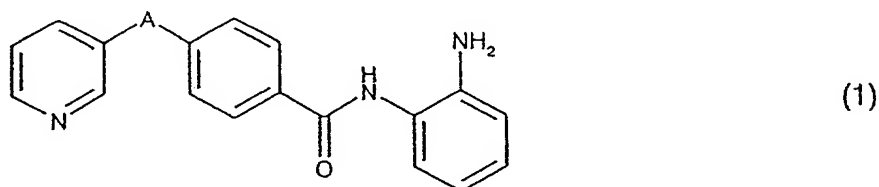
The present invention is intended to enhance the stability of compositions containing as an active ingredient a pharmaceutically useful benzamide derivative or a pharmaceutically acceptable salt and to effectively use them as a pharmaceutical formulation.

In order to solve the above problems, intensive research was conducted on the effects of temperature, humidity, and physicochemical properties on the solutions, powders, and solid shaped products to which a benzamide derivative or a pharmaceutically acceptable salt thereof has been added. As a result, the inventors have found that the problem of instability of an active ingredient can be solved and stable and excellent pharmaceutical formulations can be produced by using selectively, among the additives commonly used for pharmaceutical formulations, those additives that do not easily induce decomposition of benzamide derivatives, adding an organic acid salt, an amino compound and an inorganic basic substance, and the like as a stabilizer, producing using the dry granulation or adjusting pH in

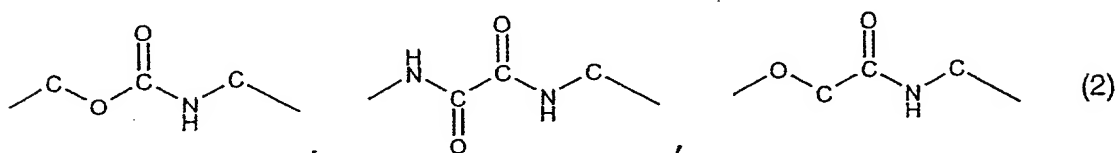
the range of 4 to 12, preferably in the range of pH 7 to 11, and thereby have completed the present invention.

Thus, the present invention relates to

[1] a pharmaceutical formulation comprising a  
5 benzamide derivative represented by the formula (1):

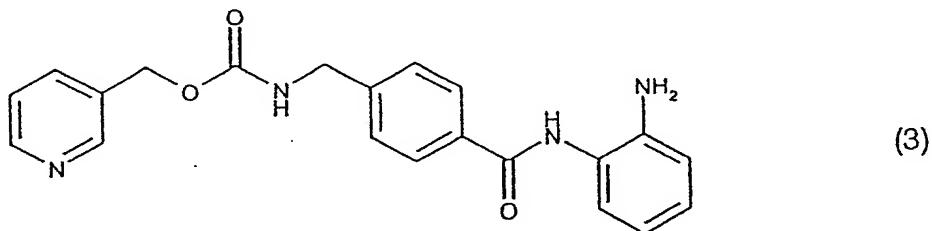


10 wherein A represents a structure shown by any one of the formula (2):



15 or a pharmaceutically acceptable salt thereof, and one or more than one additive selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent;

[2] as a preferred embodiment the pharmaceutical  
formulation of the above [1] wherein said benzamide  
20 derivative is represented by the formula (3);



[3] as a preferred embodiment the pharmaceutical  
25 formulation of the above [1] or [2] wherein said

excipient is D-mannitol;

5 [4] as another preferred embodiment the pharmaceutical formulation of any one of the above [1] to [3] wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium;

10 [5] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [4] wherein said binder is hydroxypropyl cellulose;

[6] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [5] wherein said lubricant is one or more than one selected from magnesium stearate and talc;

15 [7] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [6] wherein said coating agent is hydroxypropyl methylcellulose;

20 [8] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [7] wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol;

25 [9] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [8] wherein said formulation further comprises one or more than one selected from the group consisting of an organic acid salt, an amino compound, and an inorganic basic substance;

30 [10] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said organic acid salt is one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate;

35 [11] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said amino compound is one or more than one selected from

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the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol;

[12] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [9] wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia;

[13] as a preferred embodiment the pharmaceutical formulation of any one of the above [1] to [12] wherein the formulation is a solid formulation which comprises preparing granules by a dry granulation method; and

[14] as a preferred embodiment, the pharmaceutical formulation of any one of the above [1] to [13] wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

#### Embodiment for Carrying Out the Invention

The present invention will now be explained in further detail below.

The pharmaceutical formulations as used herein generally mean those that have been produced by formulating one or more additives with an active ingredient or active ingredients and that have been formulated into shapes suitable for use in various dosage forms of medical drugs.

According to the present invention, solid formulations, in particular powders, can be produced by adding to the active ingredient one or more than one additives that do not easily induce decomposition by using a method conventionally used by a person skilled in the art. Examples of additives that do not easily induce decomposition include: D-mannitol as an excipient; partly

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pregelatinized starch, carboxymethylstarch sodium, and  
carmellose calcium as a disintegrant; hydroxypropyl  
cellulose as a binder; magnesium stearate and talc as a  
lubricant; and hydroxypropyl methyl cellulose as a  
5 coating agent. One or more than one of them can be used.

According to the present invention, solid  
formulations, in particular granules, tablets, and  
capsules can be produced by a dry granulation method in  
which additives that do not easily induce decomposition  
10 are added to the active ingredient, mixed in a shaker  
such as a granulator and a V-type mixer, compression-  
molded by a roller compactor after the mixture in a  
shaker, and further crushed by a power mill thereby to  
form granules.

15 Furthermore, more stable granules, tablets, and  
capsules can be obtained by adding to the active  
ingredient one or more than one selected from the group  
consisting of an organic acid salt such as monosodium  
fumarate, sodium alginate, sodium dehydroacetate, sodium  
20 erythorbate, and trisodium citrate; an amino compound  
such as tris(hydroxymethyl)aminomethane,  
monoethanolamine, diethanolamine, triethanolamine,  
diisopropanolamine, triisopropanolamine,  
dihydroxyaluminum aminoacetate, arginine, creatinine,  
25 sodium glutamate, glycine, L-arginine L-glutamate, and  
carbachol; an inorganic basic substance such as sodium  
carbonate, potassium carbonate, lithium carbonate,  
strontium carbonate; ammonium carbonate, sodium  
bicarbonate, potassium bicarbonate, lithium bicarbonate,  
30 strontium bicarbonate, sodium hydroxide, disodium  
phosphate, and ammonia, and by granulating in the dry  
granulation method.

When an organic acid salt, an amino compound or an  
inorganic basic substance is added, additives such as  
35 excipients, disintegrants, binders, lubricants, and  
coating agents can be used without limitation. Examples  
include, lactose, lactose anhydride, D-mannitol, corn

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starch, and crystalline cellulose as an excipient; hydroxypropyl cellulose, polyvinylpyrrolidone, methyl cellulose, glycerin, and water as a binder; carmellose, calcium carmellose, low-substitution hydroxypropyl cellulose, and partly pregelatinized starch as a disintegrant; magnesium stearate, calcium stearate, stearic acid, and talc as a lubricant; and hydroxypropyl methyl cellulose, methacrylic acid copolymer, and hydroxypropyl methyl cellulose phthalate as a coating agent.

In accordance with the present invention, stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving an active ingredient into solvents that do not easily induce the decomposition of the active ingredient such as propylene glycol and dimethylacetamide, by using a method conventionally used by a person skilled in the art.

More stable liquids, syrups, injections, emulsions, suspensions, suppositories, soft capsules whose contents are liquid, or hard capsules whose contents are liquid and the like can be produced by dissolving in a solvent one or more than one ingredients, selected from the group consisting of an organic acid salt such as monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate and trisodium citrate; an amine compound such as tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, potassium carbonate, lithium carbonate, strontium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, strontium bicarbonate, sodium hydroxide and ammonia, and by adjusting pH in the

range of 4 to 12 with an acid or a base.

As used herein, acids or bases mean organic bases, inorganic bases, organic acids, or inorganic acids that can be used as medical drugs. Organic bases mean  
5 tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine, arginine, and the like. Inorganic bases mean sodium hydroxide, ammonium water, potassium bicarbonate, potassium carbonate, sodium bicarbonate,  
10 sodium carbonate, and the like. Organic acids mean citric acid, succinic acid, acetic acid, tartaric acid, lactic acid, and the like. Inorganic acids mean hydrochloric acid, sulfuric acid, phosphoric acid and the like.

15 In order to produce lyophilized formulations, according to the present invention, an active ingredient is mixed with a conventionally known solvent such as one or more than one solvent selected from the group consisting of purified water, macrogol, propylene glycol, polysorbate and dimethylacetamide; to a resulting  
20 composition are further added one or more than one additive selected from the group consisting of sugars; gelatin; dextrin; an organic acid salt such as monosodium fumarate, sodium alginate, sodium glutamate, sodium  
25 dehydroacetate, sodium erythorbate, trisodium citrate, and arginine-glutamate; an amine compound such as tris(hydroxymethyl)aminomethane, ammonia water, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine,  
30 dihydroxyaluminum aminoacetate, arginine, creatinine, glycine, and carbachol; an inorganic basic substance such as ammonium carbonate, disodium phosphate, sodium carbonate, sodium bicarbonate and potassium bicarbonate; and then pH of the resulting composition is adjusted to 4  
35 to 12, as desired, with an acid or a base, and the composition is freeze-dried under a reduced pressure.

The pharmaceutical formulations of the present

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invention can be administered by any method depending on various dosage forms, the age and sex of the patient, the severity of disease, and other conditions. For example, tablets, pills, liquids, syrups, suspensions, emulsions, granules, and capsules may be orally administered, injections may be intravenously administered either singly or in an admixture with a conventional supplement such as glucose and an amino acid, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Lyophilized formulations reconstituted with solvent such as saline and purified water may be administered intravenously singly or in an admixture with a conventional supplement such as glucose, an amino acid and the like, and, as needed, may be administered singly intramuscularly, subcutaneously, or intraperitoneally. Suppositories may be directly administered intrarectally.

Dosages of the pharmaceutical formulations of the present invention are selected as appropriate depending on the method of administration, the age and sex of the patient, the severity of disease, and the like. Generally the daily dosage of an active ingredient compound is preferably in the range of about 0.0001 to 100 mg/kg, and for pharmaceutical formulations in the unit dosage form an active ingredient compound is preferably included at a range of about 0.001 to 1,000 mg.

Benzamide derivatives, active ingredients of the present invention, or pharmaceutically acceptable salts thereof can be produced by a method described in, for example, Japanese Unexamined Patent Publication (Kokai) No. 10-152462.

Medical drugs as used herein mean, in addition to anticancer agents, agents for the treatment and/or amelioration of autoimmune diseases, skin diseases, infections, diseases of blood vessels, allergic diseases, gastrointestinal disorders, hormonal diseases, diabetes

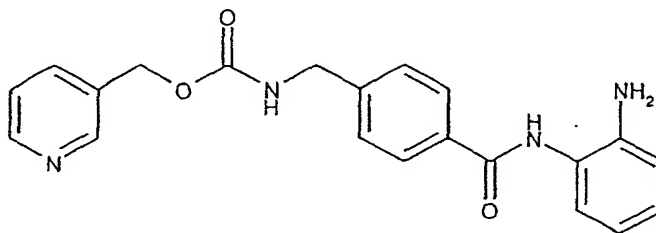
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mellitus, and the like, enhancers of the effect of gene therapy, or immunosuppressants.

#### Examples

The present invention will now be explained in more detail with reference to the following compound, N-(2-aminophenyl)-4-[N-(pyridine-3-yl)methoxycarbonyl]aminomethyl benzamide (compound 1), in Examples and Reference Examples. It is to be noted, however, that the present invention is not limited by these examples in any way.

Compound 1



#### Example 1.

Compound 1 (1 g) was mixed with 1 g each of D-mannitol, partly pregelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate, and talc to prepare a powder formulation. Similarly, lactose, corn starch, crystalline cellulose, carmellose, light-weight silicic acid anhydride, magnesium aluminum metasilicate, and titanium oxide were mixed to prepare a comparative control sample. After these formulations were stored at an air-tight condition at 60°C for 4 weeks and at an open condition at 40°C and at a relative humidity of 75% for 3 months, they were subjected to HPLC analysis. The percentage (%) of degradation products relative to the active ingredient was shown in Table 1. The powder formulation prepared by mixing 1:1 with D-mannitol, partially gelatinized starch, carmellose calcium, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, magnesium stearate or talc was stable.

Table (1): Stability of various powders

Additive	Storage condition	
	60°C air-tight 4 weeks	40°C 75% RH open 3 months
Comparative control sample		
None	0.18	0.19
Lactose	0.55	0.44
Corn starch	0.39	0.34
Crystalline cellulose	0.25	0.61
Carmellose	0.43	0.41
Light-weight silicic acid anhydride	5.87	10.01
Magnesium aluminum metasilicate	17.94	5.45
Titanium oxide	1.75	0.82
Example		
D-mannitol	0.21	0.21
Partially gelatinized starch	0.21	0.34
Carmellose calcium	0.30	0.21
Hydroxypropyl cellulose	0.20	0.20
Magnesium stearate	0.22	0.20
Hydroxypropyl methyl cellulose	0.27	0.21
Talc	0.36	0.23

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

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Example 2.

Pharmaceutical formulations a, b, c, d, e, and f shown in Table (2) were prepared in the following procedure. Thus, compound 1 and D-mannitol divided into 1/8, 2/8, and 5/8 of the prescribed amount were serially added under mixing using a granulator to prepare homogeneous powders. Furthermore, 1/2 of the prescribed amount of magnesium stearate was added thereto and was mixed in a V-shaped mixer for 20 minutes, compression-molded by a roller compactor, and further crushed by a power mill to prepare granules. Subsequently, carboxymethyl starch sodium of the prescribed amount and 1/2 of the prescribed amount of magnesium stearate were added and mixed in a V-shaped mixer, made into tablets by tableting machine to obtain samples a, b, c, d, e, and f.

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Table (2): Formulation for tablets (unit: mg)

Ingredient/number	Sample of the present invention					
	a	b	c	d	e	f
Active ingredient	5.0	1.0	1.0	1.0	1.0	1.0
D-mannitol	56.0	60.0	60.0	60.0	60.0	60.0
Carboxymethyl starchsodium	3.3	3.3	3.3	3.3	3.3	3.3
Magnesium stearate	0.7	0.7	0.7	0.7	0.7	0.7
Tris(hydroxymethyl) aminomethane	-	-	0.5	-	-	-
Potassium bicarbonate	-	-	-	0.5	-	-
Sodium carbonate	-	-	-	-	0.5	-
Potassium carbonate	-	-	-	-	-	0.5
Total	65.0	65.0	65.5	65.5	65.5	65.5

Reference Example 1.

5 D-mannitol, partially gelatinized starch; carmellose calcium, magnesium stearate, hydroxypropyl cellulose, polyvinylpyrrolidone K30, or the like which is comparatively stable when mixed with Compound 1 was granulated according to the formulation shown in Table (3) by the wet granulation method and made into tablets by tabletting machine to obtain samples g to i.

Table (3): Formulation for tablets (unit: mg)

Ingredient/number	Sample		
	g	h	i
Active ingredient	1.0	1.0	1.0
D-mannitol	40.6	40.6	40.6
Partially gelatinized starch	17.4	17.4	17.4
Hydroxypropyl cellulose	2.0	2.0	-
Polyvinylpyrrolidone	-	-	2.0
Carmellose calcium	3.3	-	3.3
Magnesium stearate	0.7	0.7	0.7
Total	65.0	65.0	65.0

15 The percentage (%) of degradation products of compound 1 is shown in Table 4, when samples obtained in Example 2 and Reference Example 1 were stored at an air-tight condition at 60°C for 4 weeks and at an air-tight condition at 80°C for 3 days, and then were subjected to HPLC analysis. The pharmaceutical formulations containing 1 mg of an active ingredient obtained by the wet granulation method shown in Reference Example 1 were 20 unstable as they produced degradation products other than the hydrolyzates, while the samples of the present

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invention shown in Example 2, both 5.0 mg- and 1.0 mg- containing formulations, were stable as the production of degradation products remained low.

Table (4): Stability of tablets containing compound 1

Sample		Content (mg)	Storage condition	
			60°C air-tight 4 weeks (%)	80°C air-tight 3 days (%)
The invention sample	a	5.0	0.4	0.4
	b	1.0	1.0	1.3
	c	1.0	0.7	0.5
	d	1.0	-	0.4
	e	1.0	-	0.4
	f	1.0	-	0.4
Reference example	g	1.0	4.1	3.0
	h	1.0	4.5	2.1
	i	1.0	5.8	5.3

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

### Example 3.

Compound 1 was dissolved to a concentration of 20 mg/ml in propylene glycol or dimethylacetamide to prepare liquid formulations. As comparative control samples, compound 1 was dissolved to a concentration of 20 mg/ml in polysorbate 80 or polyethylene glycol 400. Table (5) shows the percentage (%) of degradation products of compound 1 when these formulations were stored at an air-tight condition at 80°C for 3 days. They exhibited good stability when dissolved in propylene glycol or dimethylacetamide.

Table (5): Stability when dissolved in various solvents

Additive	Amount of degradation products (%)
Polysorbate 80	18.1
Polyethylene glycol 400	41.4
Dimethylacetamide	4.1
Propylene glycol	3.6

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

### Example 4.

Compound 1 was dissolved to a concentration of 20 mg/ml in polyethylene glycol 400 to prepare a liquid formulation, which was set as a comparative control sample. To the comparative control sample was added each  
5 additive at a concentration of 0.05 M to prepare the liquid formulation of the present invention. Table (6) shows the percentage (%) of degradation products of the active ingredients when these formulations and the comparative control samples were stored at an air-tight  
10 condition at 80°C for 3 days. Stability was enhanced in the samples to which an organic acid salt, an amino compound, or an inorganic basic substance of the present invention was added.

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Table (6): Stability of liquid formulations in which each additive was blended at 0.05 M to compound 1 at 20 mg/ml polyethylene glycol 400 (Storage condition: 80°C, air tight, Storage period: 3 days)

	Additive	Amount of degradation products (%)	pH
Comparative control sample	None	41.4	5.3
The invention sample	Sodium fumarate	21.6	7.0
	Sodium alginate	23.7	6.7
	Sodium dehydroacetate	13.0	8.6
	Sodium erhsorbate	13.2	7.3
	Trisodium citrate	28.2	8.0
	Tris (hydroxymethyl) aminomethane	2.9	10.1
	Monoethanolamine	4.3	11.5
	Diethanolamine	3.9	11.7
	Triethanolamine	9.6	9.4
	Diisopropanolamine	4.7	9.9
	Triisopropanolamine	16.5	8.3
	Dihydroxyaluminum aminoacetate	7.3	6.4
	L-arginine	10.6	11.5
	Creatinine	18.6	7.0
	Sodium glutamate	23.1	-
	Glycine	26.7	-
	L-arginine L-glutamate	29.4	6.5
	Carbachol	32.3	5.4
	Ammonium carbonate	3.6	10.7
	Disodium phosphate	10.8	7.6
	Sodium carbonate	16.8	10.1
	Sodium bicarbonate	25.0	6.5
	Potassium bicarbonate	15.5	7.0
	Ammonia	4.6	11.7

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

#### 10 Example 5.

To compound 1 dissolved at a concentration of 20 mg/ml in polyethylene glycol 400 was added an equal volume of 0.1 M tris(hydroxymethyl)aminomethane buffer of which pH is varied with hydrochloric acid or sodium hydroxide to prepare a liquid formulation of compound 1 at 10 mg/ml. Table 7 shows the percentage of the degradation products of the active ingredient when these formulations were stored at an air-tight condition at

80°C for 3 days. Samples of the present invention of which pH was adjusted in the range of 7 to 11 exhibited good stability.

Table (7): Stability of 10 mg/ml polyethylene glycol 400 solution of compound 1 when pH was varied (storage condition: 80°C, air-tight, storage period: 3 days).

pH	Amount of degradation products (%)
3.8	98.6
13.2	48.8
7.3	11.9
7.7	8.2
8.5	5.8
9.5	5.6
10.1	4.4

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

Example 6.

Compound 1 was dissolved at a concentration of 20 mg/ml in polyethylene glycol 400, and sodium hydroxide was added thereto so that the final various concentrations can be from 0 mM to 10 mM to prepare liquid formulations. Table 8 shows the percentage of the degradation products of the active ingredient when these formulations were stored at each pH of these formulations and at an air-tight condition at 80°C for 1 day or 7 days. Samples of the present invention of which pH was adjusted in the range of about 7 to 11 exhibited good stability.

Table (8): Relationship between pH and stability of liquid formulations in which compound 1 was dissolved at 20 mg/ml in polyethylene glycol 400, and then sodium hydroxide was added thereto

5 (storage condition: 80°C, air-tight, storage period: 1 day or 7 days)

Concentration of sodium hydroxide (mM)	pH	Amount of degradation products (%)	
		80°C - 1 day	80°C - 7 days
0	5.3	16.0	63.7
0.01	5.9	14.1	60.6
0.1	6.1	14.3	56.0
1.0	7.3	9.7	33.7
2.0	8.9	4.6	12.4
3.0	9.4	5.0	9.8
4.0	10.4	6.0	9.7
5.0	10.8	9.7	11.4
10.0	13.1	71.5	90.6

Figures in the table represent the total amount (%) of the degradation products produced by the decomposition of compound 1.

10

#### Industrial Applicability

Pharmaceutical formulations that produce little degradation products and that are stable enough to be used as medical drugs can be obtained by mixing a pharmaceutically useful benzamide derivatives or a pharmaceutically acceptable salt thereof with additives that do not easily produce degradation products, blending an organic acid salt, an amine compound, or an inorganic basic substance, producing solid formulations by the dry granulation method, and further adjusting the pH of the liquid formulations to 4 to 12.

20

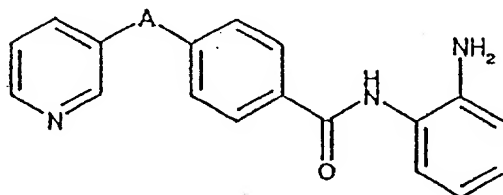
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AMENDED CLAIMS

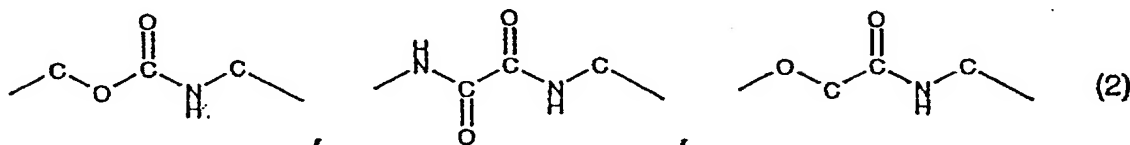
1. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



(1)

5

wherein A represents a structure shown by any one of the formula (2):



(2)

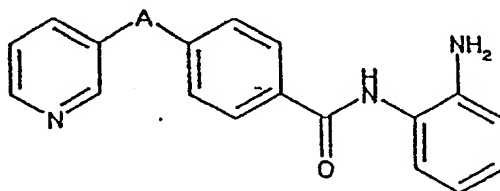
10

or a pharmaceutically acceptable salt thereof, (ii) one or more than one selected from the group consisting of an organic acid salt, an amino compound and an inorganic basic substance, and (iii) one or more than one selected from the group consisting of an excipient, a disintegrant, a binder, a lubricant, a coating agent and a solvent.

15

20

2. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):

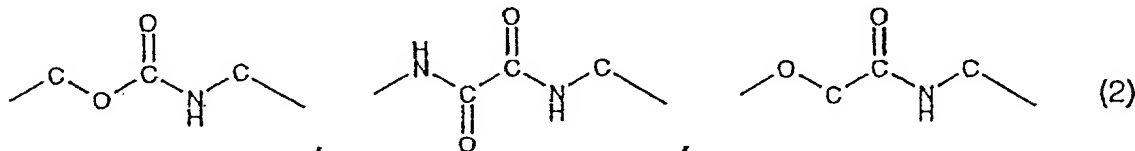


(1)

25

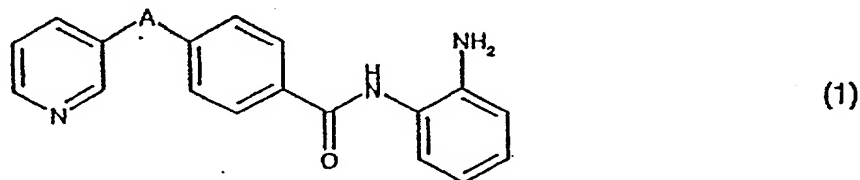
wherein A represents a structure shown by any one of the formula (2):

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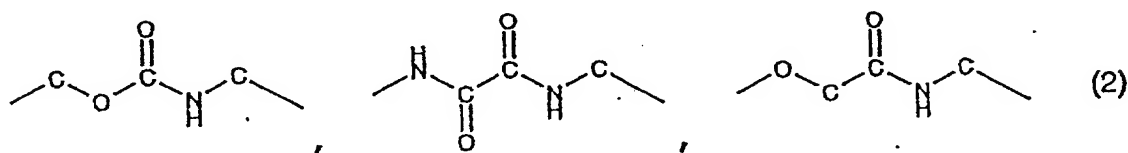


or a pharmaceutically acceptable salt thereof, and (ii) one or more than one selected from the group consisting of D-mannitol, partially gelatinized starch, carboxymethylstarch sodium, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose and dimethylacetamide.

10. 3. A pharmaceutical formulation comprising (i) a benzamide derivative represented by the formula (1):



15. wherein A represents a structure shown by any one of the formula (2):

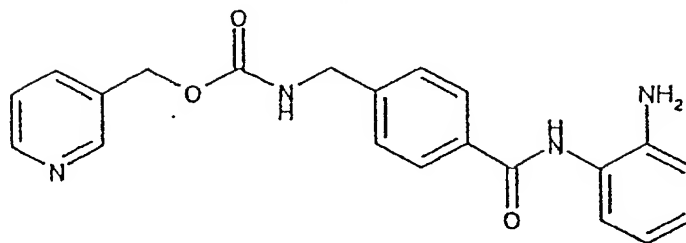


20. or a pharmaceutically acceptable salt thereof, wherein said benzamide derivative or pharmaceutically acceptable salt thereof is dissolved in propylene glycol.

25. 4. The pharmaceutical formulation according to any one of claims 1 to 3 wherein said benzamide derivative is represented by the formula (3):

## Replacement Sheet

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5. The pharmaceutical formulation according to claims 1, 2 and 4 wherein said pharmaceutical formulation is a solid formulation.

6. The pharmaceutical formulation according to claims 1 to 4 wherein said pharmaceutical formulation is a liquid formulation.

7. The pharmaceutical formulation according to claims 1, 4 and 5 wherein said excipient is D-mannitol.

8. The pharmaceutical formulation according to any one of claims 1, 4, 5 and 7 wherein said disintegrant is one or more than one selected from the group consisting of partly pregelatinized starch, carmellose calcium, and carboxymethylstarch sodium.

9. The pharmaceutical formulation according to any one of claims 1, 4, 5, 7 and 8 wherein said binder is hydroxypropyl cellulose.

10. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 9 wherein said lubricant is one or more than one selected from magnesium stearate and talc.

11. The pharmaceutical formulation according to claims 1, 4, 5 and 7 to 10 wherein said coating agent is hydroxypropyl methylcellulose.

12. The pharmaceutical formulation according to claims 1, 4 and 6 wherein said solvent is one or more than one selected from the group consisting of propylene glycol, dimethylacetamide, and polyethylene glycol.

13. The pharmaceutical formulation according to claims 1 and 4 to 12 wherein said organic acid salt is

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one or more than one selected from the group consisting of monosodium fumarate, sodium alginate, sodium dehydroacetate, sodium erythorbate, and trisodium citrate.

5           14. The pharmaceutical formulation according to claims 1 and 4 to 13 wherein said amino compound is one or more than one selected from the group consisting of tris(hydroxymethyl)aminomethane, monoethanolamine, diethanolamine, triethanolamine, diisopropanolamine, 10 triisopropanolamine, dihydroxyaluminum aminoacetate, arginine, creatinine, sodium glutamate, glycine, L-arginine L-glutamate and carbachol.

15           15. The pharmaceutical formulation according to claims 1 and 4 to 14 wherein said inorganic basic substance is one or more than one selected from the group consisting of sodium carbonate, potassium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, disodium phosphate, and ammonia.

20           16. The pharmaceutical formulation according to claims 1, 2, 4, 5, 7 to 11 and 13 to 15 wherein the formulation is a solid formulation which comprises granules prepared by a dry granulation method.

25           17. The pharmaceutical formulation according to claims 1 to 4, 6 and 12 to 15 wherein the formulation is a liquid formulation and pH is adjusted within the range of 4 to 12.

ABSTRACT

Stable pharmaceutical formulations can be obtained  
by mixing a pharmaceutically useful benzamide derivative  
5 or a pharmaceutically acceptable salt thereof with  
additives that do not easily produce degradation  
products, blending an organic acid salt, an amine  
compound, and an inorganic basic substance, producing  
solid formulations by the dry granulation method, and  
10 further adjusting the pH of the liquid formulations to 4  
to 12. Pharmaceutical formulations that produce little  
degradation products and that are stable enough to be  
used as medical drugs can be obtained.

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## Japanese Language Declaration

## 日本語宣言書

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My residence, post office address and citizenship are as stated next to my name.

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I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PHARMACEUTICAL AGENT COMPRISING A BENZAMIDE

DERIVATIVE AS ACTIVE INGREDIENT

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I hereby claim foreign priority under Title 35, United States Code, Section 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application for which priority is claimed.

Prior Foreign Application(s)

外国での先行出願

Priority Not Claimed

優先権主張なし

11-229551 (Pat. Appln.)

Japan

16/August/1999

(Number)  
(番号)(Country)  
(国名)(Day/Month/Year Filed)  
(出願日/月/年)☐(Number)  
(番号)(Country)  
(国名)(Day/Month/Year Filed)  
(出願日/月/年)☐

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(Application No.)  
(出願番号)(Filing Date)  
(出願日)(Application No.)  
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(出願番号)(Filing Date)  
(出願日)(Status: Patented, Pending, Abandoned)  
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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (list name and registration number).

書類送付先

Send Correspondence to:

Morgan, Lewis & Bockius LLP  
1800 M Street, N.W.  
Washington, D.C. 20036-5869

Customer Number: 009629

直通電話連絡先: (氏名及び電話番号)

Direct Telephone Calls to: (name and telephone number)

**Robert J. Gaybrick**  
**202-467-7000**

唯一または第一発明者氏名

Full name of sole or first inventor

1-0 Tsuneji Suzuki

発明者の署名

日付

Inventor's signature

Date February 6,

TSUNEJI SUZUKI, 2002

住所

Residence

Mobara-shi, Chiba Japan SPX

国籍

Citizenship

Japanese

郵便の宛先

Post Office Address

TSUNEJI SUZUKI

c/o Mitsui Chemicals, Inc., 1144,

Togo, Mobara-shi, Chiba 297-0017, Japan

第二共同発明者がいる場合、その氏名

Full name of second joint inventor, if any

2-0 Tomoyuki Ando

第二共同発明者の署名

日付

Second inventor's signature

Date

TOMOYUKI ANDO February 6, 2002

住所

Residence

Mobara-shi, Chiba Japan SPX

国籍

Citizenship

Japanese

郵便の宛先

Post Office Address

c/o Mitsui Chemicals, Inc., 1144,

Togo, Mobara-shi, Chiba 297-0017,

Japan

(第三以下の共同発明者についても同様に記載し、署名すること)

(Supply similar information and signature for third and subsequent joint inventors.)

第三共同発明者	3-D	Full name of third joint inventor, if any <u>Masahiko Ishibashi</u>	
第三共同発明者	日付	Third inventor's signature <u>Masahiko Ishibashi</u>	Date February 6, 2002
住 所		Residence <u>Mobara-shi, Chiba/ Japan</u> <u>SPX</u>	
国 籍		Citizenship Japanese	
私書箱		Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1, Togo, Mobara-shi, Chiba 297-0017, Japan	
第四共同発明者	4-D	Full name of fourth joint inventor, if any <u>Masahiro Sakabe</u>	
第四共同発明者	日付	Fourth inventor's signature <u>Masahiro Sakabe</u>	Date February 6, 2002
住 所		Residence <u>Mobara-shi, Chiba/ Japan</u> <u>SPX</u>	
国 籍		Citizenship Japanese	
私書箱		Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1, Togo, Mobara-shi, Chiba 297-0017, Japan	

第五共同発明者	5-D	Full name of fifth joint inventor, if any <u>Ikuo Sakai</u>	
第五共同発明者	日付	Fifth inventor's signature <u>Ikuo Sakai</u>	Date February 6, 2002
住 所		Residence <u>Mobara-shi, Chiba/ Japan</u> <u>SPX</u>	
国 籍		Citizenship Japanese	
私書箱		Post Office Address c/o Mitsui Pharmaceuticals, Inc., 1900-1, Togo, Mobara-shi, Chiba 297-0017, Japan	
第六共同発明者		Full name of sixth joint inventor, if any	
第六共同発明者	日付	Sixth inventor's signature	Date
住 所		Residence	
国 籍		Citizenship	
私書箱		Post Office Address	

(第七以降の共同発明者についても同様に  
記載し、署名をすること)

(Supply similar information and signature for  
seventh and subsequent joint inventors.)